

3.2 TECHNICAL ABSTRACT

The incidence of melanoma has been increasing faster than any other cancer with 56,000 cases diagnosed per year in the United States. It accounts for 1-2% per year of all cancer deaths in the U.S. Estimates project that 1 in 75 persons will develop melanoma in their lifetime. In spite of advances with combined modality therapies - including surgery, chemotherapy and immune-modulatory therapies - relapse rates are high and patients who develop metastatic disease have a poor prognosis with a median survival time of 6-7 months.

As a potential treatment for melanoma, this protocol is an investigation of a new liposome technology, termed SPLP (Stable Plasmid Lipid Particles) DNA delivery that was developed to deliver genes, in the form of plasmid DNA, to sites of tumor growth. The physical properties of SPLP allow them to circulate in the blood stream for several hours following intravenous administration and to accumulate at distal tissue sites characterized by vascular leak. Once accumulated at the disease site, the SPLP are taken up by tumor cells and their protein products are expressed. The delivered genes are preferentially expressed in the tumor tissue and not in other normal tissues, resulting in a local, tumor-selective therapy.

Pro-1, the study drug, is a liposome-encapsulated thymidine kinase gene formulation. The lipid formulation of Pro-1 is composed of four synthetic lipids: DSPC, DODMA, PEG-DSG, and cholesterol. In this study, the lipids will encapsulate a plasmid DNA encoding a thymidine kinase enzyme. The thymidine kinase gene derived from Herpes Simplex Virus (HSV-tk) encodes an enzyme that acts to catalyze the monophosphorylation of the non-toxic prodrug acyclovir (ACV). ACV monophosphate (ACV-MP) is in turn a substrate for cellular kinases that convert ACV-MP to the diphosphate and triphosphate forms. The nucleotide analogue ACV triphosphate (ACV-TP) is a substrate for DNA polymerase and acts as a chain terminator upon incorporation into newly synthesized DNA. Mitotic cells that are exposed to ACV-TP undergo apoptotic cell death. Since ACV-TP requires that cells be actively dividing in order to induce apoptosis and tumor cells are often more actively dividing than cells in normal tissue, toxicity in collateral tissue is minimized. Further selectivity is conferred by the fact that ACV is a very poor substrate for cellular kinases, limiting ACV phosphorylation to cells that have been transfected with HSV-tk.

In this phase I study, Pro-1 will be administered intravenously to patients with stage IV metastatic melanoma followed by an oral administration of Valtrex[®] (valacyclovir hydrochloride). After oral administration, Valtrex is rapidly absorbed from the gastrointestinal tract and nearly completely converted to acyclovir by first pass intestinal and/or hepatic metabolism. This clinical investigation is a single-dose escalation study whose primary objectives are to evaluate the safety and pharmacokinetics of intravenously administered Pro-1 and to evaluate the presence of delivered plasmid DNA in tumor samples of selected patients. To assess the safety of escalating doses of Pro-1, five cohorts have been designed with three patients each. The cohorts will be administered increasing doses of Pro-1 ranging from 0.0015 mg/kg DNA to 1.0 mg/kg DNA. The study will enroll patients with stage IV melanoma who have been previously treated with chemo-, radio-, and /or biologic therapies.